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Applicant:	Piet HERDEWIJN	Confirmation No.:	Not Yet Assigned
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Customer No.:	21559		
Title:	PHOSPHONATE NUCLEOSIDES USEFUL AS ACTIVE INGREDIENTS IN PHARMACEUTICAL COMPOSITIONS FOR THE TREATMENT OF VIRAL INFECTIONS, AND INTERMEDIATES FOR THEIR PRODUCTION		

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PRELIMINARY AMENDMENT

Prior to examination, kindly amend the application as follows.

AMENDMENTS TO THE SPECIFICATION

On page 1 (line 4), after the title, of PCT/BE2005/000032 (WO 2005/085268 A2; copy enclosed), please insert the following new paragraph:

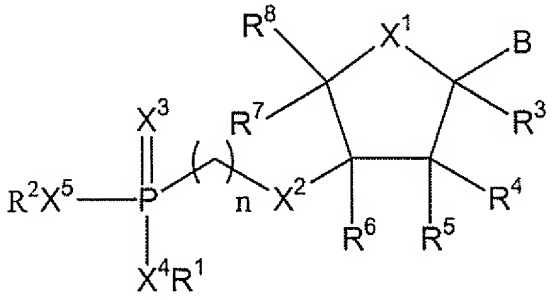
Cross-reference to related applications

This application is the U.S. National Stage of International Application No. PCT/BE2005/000032, filed March 4, 2005, which, in turn, claims the benefit of British patent application No. 0404891.4, filed March 4, 2004, British patent application No. 0407712.9, filed April 5, 2004, and U.S. provisional patent application No. 60/552,730, filed March 15, 2004.

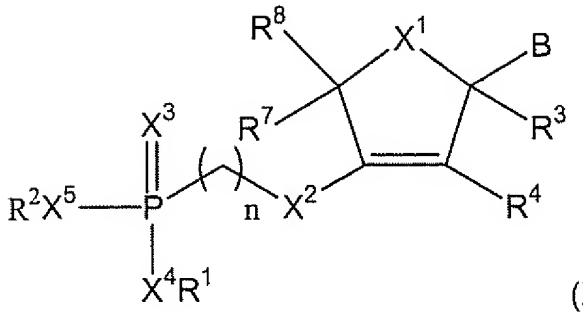
AMENDMENTS TO THE CLAIMS

1-13 (cancelled)

14. (new) A compound including a heterocyclic nucleobase attached to a first carbon atom of an optionally substituted five-member saturated or mono-unsaturated heterocyclic group selected from tetrahydrofuranyl, tetrahydrothienyl, dihydrofuranyl and dihydrothienyl and further including a phosphonoalkoxy or phosphonothioalkyl group attached to a second carbon atom of said five-member saturated or mono-unsturated heterocyclic group, said first carbon atom being adjacent to the heteroatom of said five-member saturated or mono-unsturated heterocyclic group, and said second carbon atom being adjacent neither to the heteroatom nor to the first carbon atom of said five-member saturated or mono-unsturated heterocyclic group, said compound being represented by one of the general formulae (II) and (XIX):



(II), and



(XIX)

wherein:

- X^1, X^2, X^3, X^4 and X^5 are each each independently selected from the group consisting of oxygen and sulfur,
- B is a natural or non-natural heterocyclic nucleobase,
- R^1 and R^2 are each independently selected from the group consisting of hydrogen; $(-PO_3R^{16})_m-PO_3R^{17}R^{18}$; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; arylalkyl; heterocyclic; heterocyclic-alkyl; acyloxyalkyl; acyloxyalkenyl; acyloxyalkynyl; acyloxyaryl; acyloxyarylalkyl; acyloxyarylalkenyl; acyloxyarylalkynyl; dialkylcarbonate; alkylarylcarbonate; alkylalkenylcarbonate; alkylalkynylcarbonate; alkenylarylcarbonate; alkynyl-arylcarbonate; alkenylalkynylcarbonate; dialkenylcarbonate; dialkynyl-carbonate; wherein said alkyl, alkenyl and alkynyl optionally contains one or more heteroatoms in or at the end of the hydrocarbon chain, said heteroatoms being independently selected from the group consisting of oxygen, sulfur and nitrogen;
- R^3, R^4, R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, azido, halogen, cyano, alkyl, alkenyl, alkynyl, SR^{14} and OR^{14};
- R^{14} is selected from hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; heterocyclic; arylalkyl; heterocyclic-alkyl; acyloxyalkyl; wherein said

alkyl, alkenyl and alkynyl optionally contain one or more heteroatoms in or at the end of the hydrocarbon chain, said heteroatoms being independently selected from the group consisting of oxygen, sulfur and nitrogen;

- R^{16}, R^{17} and R^{18} are independently selected from the group consisting of hydrogen; alkyl; alkenyl; alkynyl; cycloalkyl; cycloalkenyl; cycloalkynyl; aryl; arylalkyl; heterocyclic ring; heterocyclic ring-alkyl; acyloxyalkyl; wherein said alkyl, alkenyl and alkynyl optionally contain one or more heteroatoms in or at the end of the hydrocarbon chain, said heteroatoms being independently selected from the group consisting of oxygen, sulfur and nitrogen;

- X^4 and R^1, or X^5 and R^2 may together form an amino-acid residue or polypeptide wherein a carboxyl function of said amino-acid residue being at a distance from the amidate nitrogen not further than 5 atoms is esterified;

- X^4 and R^1 or X^5 and R^2 may together form a group having the formula $-OC(R^9)_2OC(O)Y(R^{10})_a$ wherein Y = N or O, a = 1 when Y is O and a = 1 or 2 when Y is N;

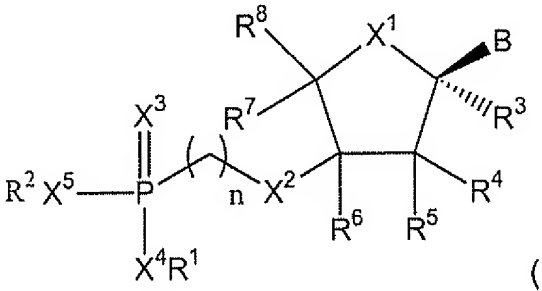
- R^9 is selected from the group consisting of hydrogen, alkyl, aryl, alkenyl, alkynyl, alkenylaryl, alkynylaryl or alkylaryl, wherein each of said alkyl, alkenyl, alkynyl and aryl groups is optionally substituted with one or more atoms or groups selected from the group consisting of halo, cyano, azido, nitro and OR^{14};

- R^{10} is selected from the group consisting of hydrogen, alkyl, aryl, alkenyl, alkynyl, alkenylaryl, alkynylaryl and alkylaryl, wherein each of said alkyl, alkenyl, alkynyl and aryl groups is optionally substituted with one or more atoms or groups selected from the group consisting of halo, cyano, azido, nitro, OR^{14} and $NR^{11}R^{12}$;

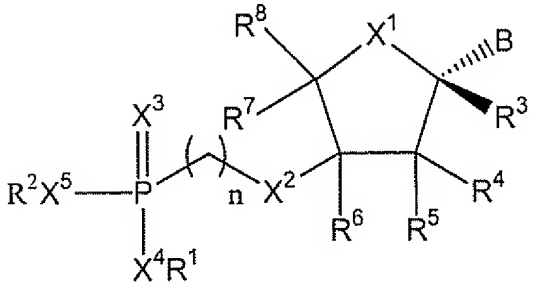
- R^{11} and R^{12} are each independently selected from the group consisting of hydrogen and alkyl, provided that at least one of R^{11} and R^{12} is not hydrogen;
- n is an integer representing the number of methylene groups between X_2 and P, each of said methylene groups being optionally and independently substituted with one or two substituents selected from the group consisting of halogen, hydroxyl, sulhydryl and C_{1-4} alkyl, and n being selected from 1, 2, 3, 4, 5 and 6; and
- m is 0 or 1,

including pharmaceutically acceptable salts, solvates, stereoisomers and prodrugs thereof.

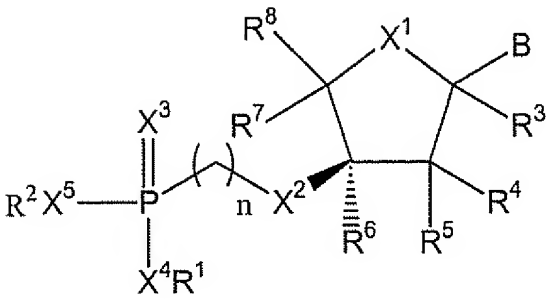
15. (new) A compound according to claim 14, being represented by one of the general formulae (III) to (XVIII):



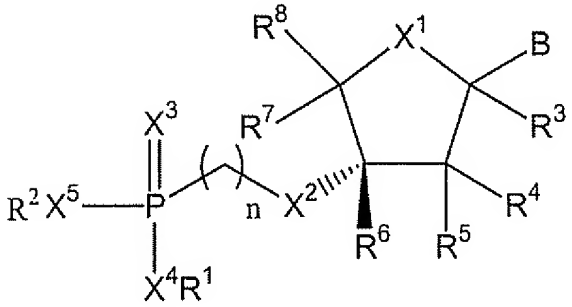
(III),



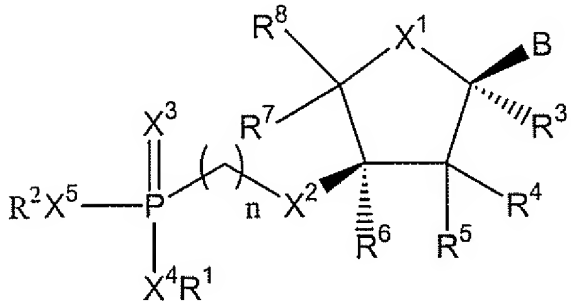
(IV),



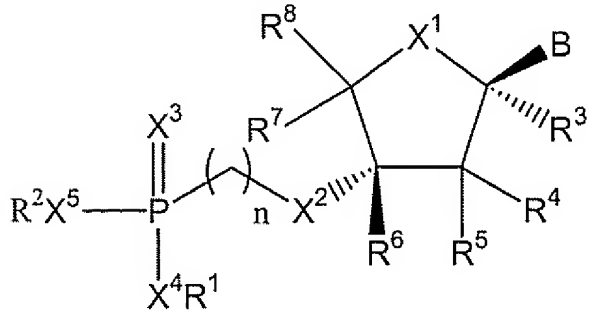
(V),



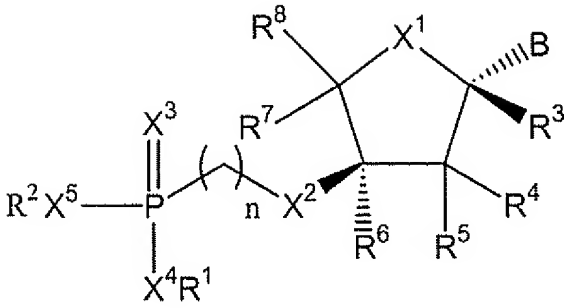
(VI),



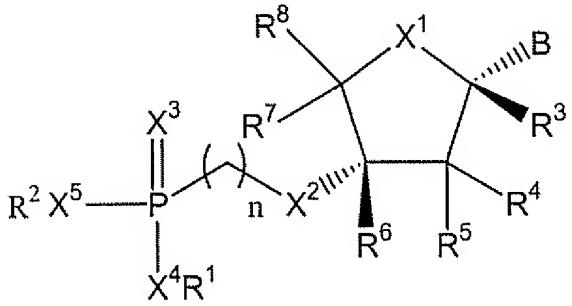
(VII),



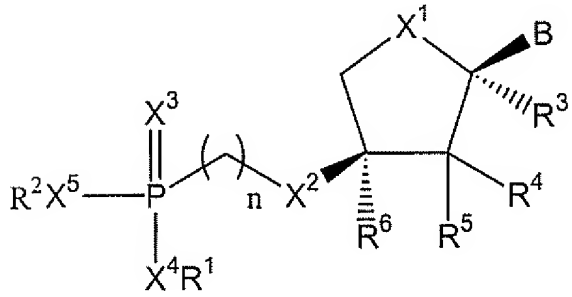
(VIII),



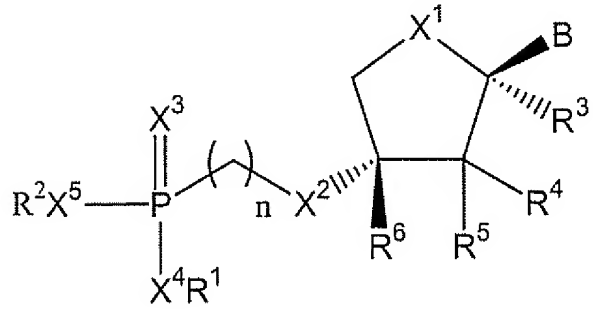
(IX),



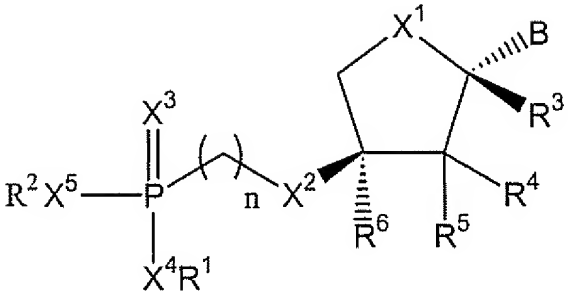
(X),



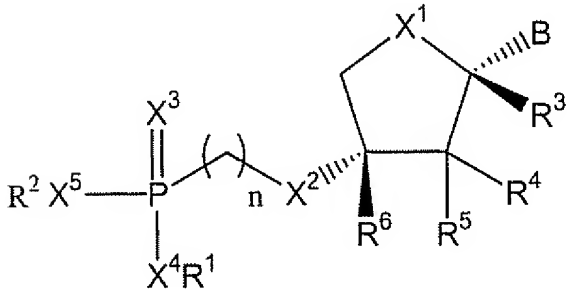
(XI),



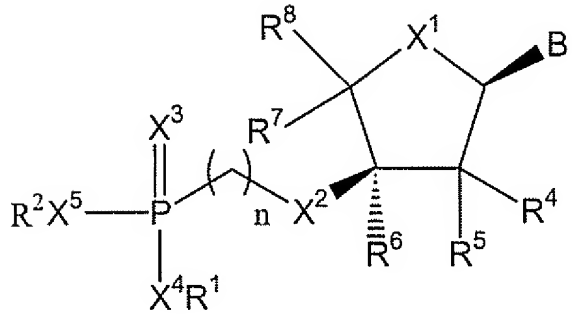
(XII)



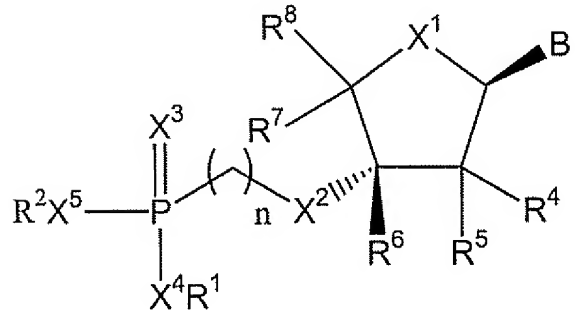
(XIII)



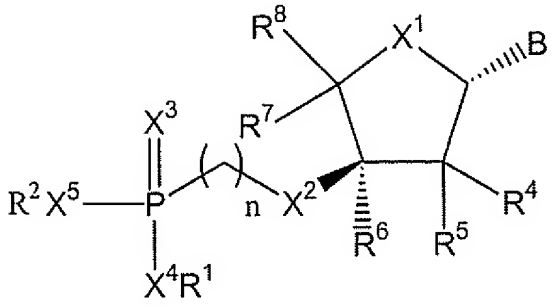
(XIV),



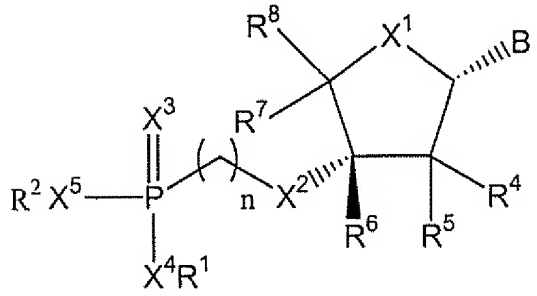
(XV),



(XVI)



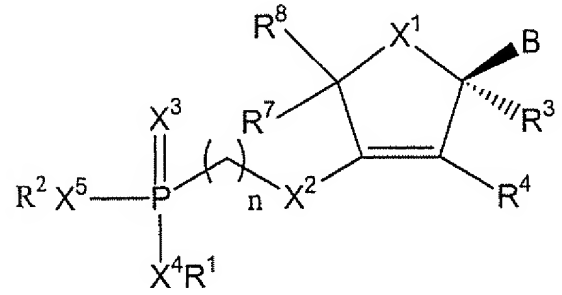
(XVII), and



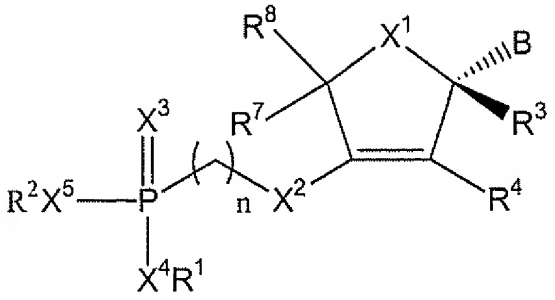
(XVIII)

wherein n, m, B, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{16}, R^{17} and R^{18} are defined as in formula (II), including pharmaceutically acceptable salts, solvates, stereoisomers and prodrugs thereof.

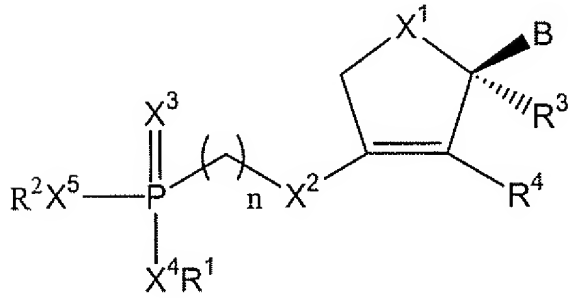
16. (new) A compound according to claim 14, being represented by any of the following formulae (XX) to (XXVI):



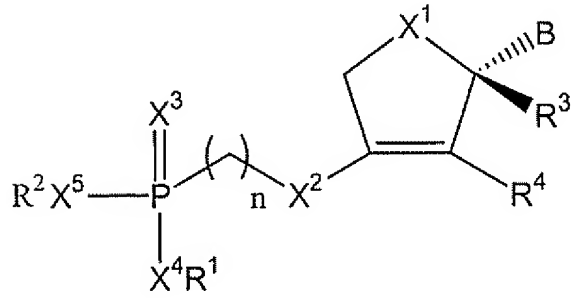
(XX),



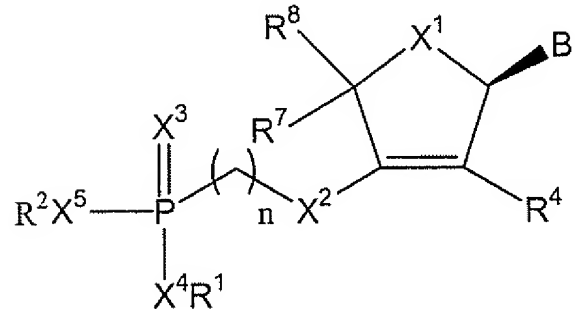
(XXI),



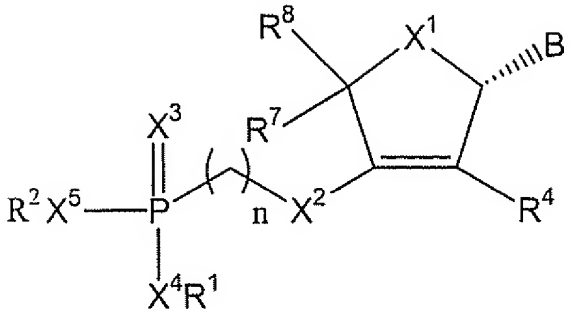
(XXII),



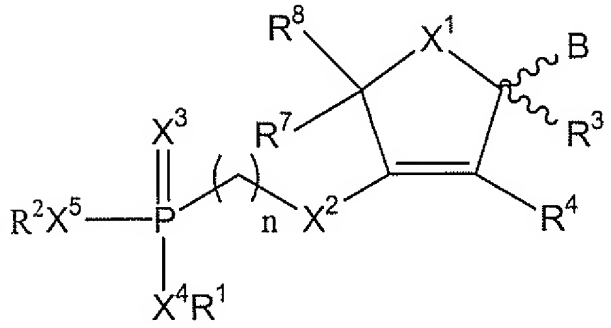
(XXIII),



(XXIV),



(XXV), and



(XXVI),

wherein n, m, B, X^1, X^2, X^3, X^4, X^5, R^1, R^2, R^3, R^4, R^7, R^8, R^9, R^{10}, R^{11}, R^{12}, R^{14}, R^{16}, R^{17} and R^{18} are defined as in formula (II), including pharmaceutically acceptable salts, solvates, stereoisomers and prodrugs thereof.

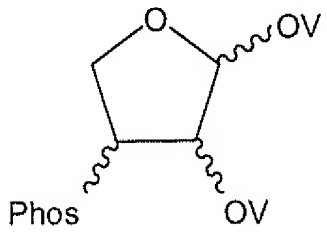
17. (new) A compound according to claim 14, wherein B is selected from the group consisting of hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine,

hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil and 5-propynyluracil.

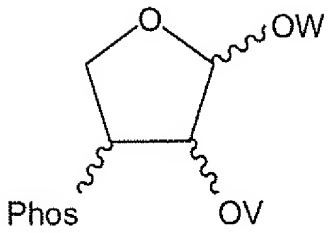
18. (new) A compound according to claim 15, wherein B is selected from the group consisting of hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil and 5-propynyluracil.

19. (new) A compound according to claim 16, wherein B is selected from the group consisting of hypoxanthine, guanine, adenine, cytosine, inosine, thymine, uracil, xanthine, 8-aza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza-8-aza derivatives of adenine, guanine, 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 1-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 7-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 3-deaza derivatives of 2-aminopurine, 2,6-diaminopurine, 2-amino-6-chloropurine, hypoxanthine, inosine and xanthine; 6-azacytosine; 5-fluorocytosine; 5-chlorocytosine; 5-iodocytosine; 5-bromocytosine; 5-methylcytosine; 5-bromovinyluracil; 5-fluorouracil; 5-chlorouracil; 5-iodouracil; 5-bromouracil; 5-trifluoromethyluracil; 5-methoxymethyluracil; 5-ethynyluracil and 5-propynyluracil.

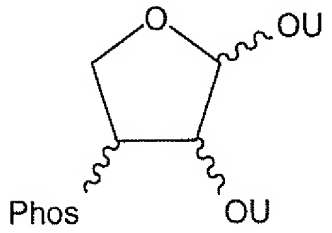
20. (new) A compound represented by one of the following general formulae (XXXI) to (XXXVI):



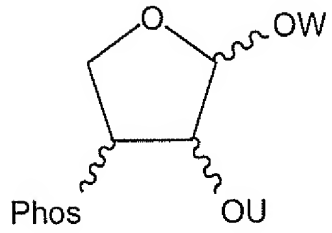
(XXXI),



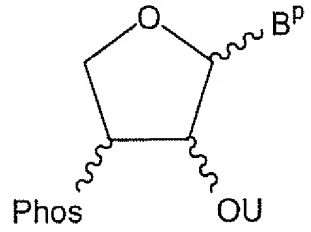
(XXXII),



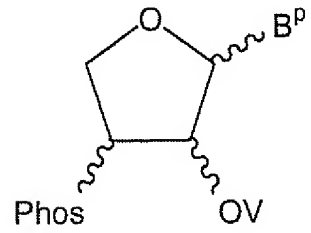
(XXXIII),



(XXXIV),



(XXXV), and



(XXXVI),

wherein:

- U is an acyl group,
- V is a silyl group,
- W is an alkyl group,
- the snake-like symbol means any stereochemical arrangement of the respective bond,
- B^p is an optionally protected heterocyclic nucleobase, and
- Phos is an O-protected phosphonoalkoxy group or phosphonothioalkyl group.

21. (new) A compound according to claim 14, being selected from the group consisting of:

1-(N^6-benzoyladenin-9-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**11**);

1-(thymin-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose(**12**);

1-(uracil-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**13**);

1-(N^4-acetylcytosin-1-yl)-2-O-benzoyl-3-O-(diisopropylphosphonomethyl)-L-threose (**14**);

1-(adenin-9-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**15**);

1-(thymin-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**16**);

1-(uracil-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**17**);

1-(cytosin-1-yl)-3-O-(diisopropylphosphonomethyl)-L-threose (**18**);

1-(adenin-9-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**19**);

1-(thymin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**20**);

1-(uracil-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**21**);

1-(cytosin-1-yl)-2-deoxy-3-O-(diisopropylphosphonomethyl)-L-threose (**22**);

1-(adenin-9-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3a**);

1-(thymin-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3b**);

1-(uracil-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3c**);

1-(cytosin-1-yl)-3-O-(phosphonomethyl)-L-threose sodium salt (**3d**);

1-(adenin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3e**);

1-(thymin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3f**);

1-(uracil-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3g**);

1-(cytidin-1-yl)-2-deoxy-3-O-(phosphonomethyl)-L-threose sodium salt (**3h**);

a pharmaceutically acceptable salt , an stereoisomer, a solvate or a pro-drug thereof.

22. (new) A method of prevention or treatment of a viral infection in a mammal comprising the administration of a compound according to claim 14.

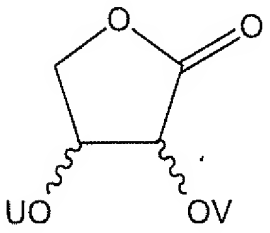
23. (new) A method of prevention or treatment of an infection by the Human Immunodeficiency Virus (HIV) comprising the administration of a compound according to claim 14.

24. (new) A pharmaceutical composition comprising a compound according to claim 14 as an active ingredient in admixture with at least a pharmaceutically acceptable

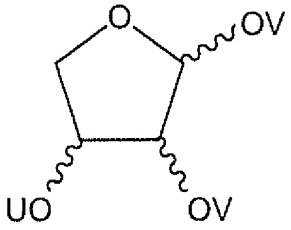
carrier.

25. (new) A pharmaceutical composition comprising a compound according to claim 14 as an active ingredient in admixture with at least a pharmaceutically acceptable carrier, and further comprising an antiviral agent.

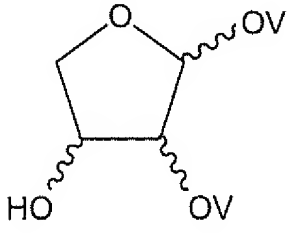
26. (new) A compound represented by one of the following general formulae (XXVIII) to (XXX):



(XXVIII),



(XXIX), and



(XXX),

wherein:

- U is an acyl group,
- V is a silyl group, and
- the snake-like symbol means any stereochemical arrangement of the respective bond.

REMARKS

Applicants herewith file, without prejudice, a new set of claims to substitute the claims as appended to the International Preliminary Report on Patentability mailed May 23, 2006 (copy enclosed). Applicants note that there is no intention to abandon any subject matter with regard to any deleted matter. Applicants also amend the specification to cross-reference related applications. A courtesy copy of the present specification is enclosed, but the World Intellectual Property Office (WIPO) copy should be relied upon if it is already present in the U.S. Patent and Trademark Office file. No new matter has been added by the present amendment.

If there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

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